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Interferon beta-1b injection site reactions and necroses

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We conducted a comprehensive review of selected adverse event reports that were submitted to the Food and Drug Administration (FDA) for interferon beta-1b during the first 30 months following licensure. The adverse events reviewed were injection site reactions, injection site necroses, and non-injection site necroses. These adverse events were selected because of the relative frequency of injection site reactions and because of the severity and sequelae of certain injection site and non-injection site necroses. Our review enabled us to characterize the clinical presentation and the treatment received, which were not described in the package insert or by the IFNB (interferon beta-1b) Multiple Sclerosis Study Group publication. The time of onset of the adverse events ranged from 1-29 months after initiation of interferon beta-1b treatment, with a mean of 1 month. In general, the more clinically significant adverse events (i.e., injection site necrosis and non-injection site necrosis) developed more slowly than the injection site reactions. Greater than 85% of the adverse events presented with one or two signs/symptoms, although the number of signs/symptoms ranged from 1-8. No predominance of treatments for the adverse events was observed. The most striking finding was that the overall sex ratio, which could be due to reporting artifacts, was 8.1: 1 female: male.

Keywords interferon beta-1b adverse events

Introduction

Interferon beta-1b was licensed by the Food and Drug Administration (FDA) in July 1993 for use in decreasing the frequency of clinical exacerbations in relapsing-emitting multiple sclerosis. Since that time, numerous adverse event reports have been submitted to FDA for interferon beta-1b. Among those were adverse event reports for injection site reactions, injection site necroses, and non-injection site necroses. Because of the relative severity and possible serious sequelae of the injection site necroses and non-injection site necroses in particular, we reviewed the reports available in the FDA database as to the frequencies, clinical presentations, treatments received, and, when possible, outcomes of these adverse events. We believe that the results of our review are of clinical relevance and will be useful to neurologists who manage multiple sclerosis patients receiving interferon beta-1b.

Methods

FDA receives adverse event reports from two sources: (1) manufacturers, who are required by Federal regulation to submit to FDA all adverse events known to them for FDA-licensed products, and (2) individuals (e.g., physicians, pharmacists, patients), who report adverse events to FDA on a voluntary basis, whether as private persons or on behalf of health care institutions. The source of the data for this review consisted of all interferon beta-1b adverse event reports received by FDA and entered into FDA's

database between July 1993 and January 1996, representing the first 30 months post-licensure of interferon beta-1b.

The criteria for selection of 'interferon beta-1b adverse event reports for this review' were: (1) 'key words' (i.e., used to index each adverse event report in FDA's database) that denoted injection site reactions, 'injection site necroses, and/or non-injection site necroses and (2) the retrievability of a hard copy of the adverse event report, either from FDA's post-licensure adverse event reviewer for interferon beta-1b or from the FDA database archives.

Injection site reactions were defined as localized reactions such as erythema or pain and excluded necrosis; Non-injection site necroses were distant from the injection site (e.g., fingers, forearms, genitourinary mucosa).

The data tabulated from each adverse event report included patient age, patient sex, and length of interferon beta-1b treatment at the time of onset of the adverse event. Due to widely varying degrees of detail provided in the adverse event reports [e.g., patient reported injection site reactions a couple of weeks after starting interferon beta-1b), the time to onset could be uniformly determined across all reports only in monthly increments. Other information selected included the clinical presentation of each adverse event (e.g., bruising, ulceration, necrotizing fasciitis), the treatment received for each adverse event (e.g., steroids, antibiotics, surgery, not indicated), and the clinical outcome of each adverse event (e.g., resolved, indeterminate). The treatment received for each adverse event could be uniformly determined only overall, not whether any of multiple treatments received were concurrent or sequential.

The percentage of missing data is noted in the Results section. Duplicate adverse event reports [e.g.,

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Received 15 July 1997; revised 24 October 1997; accepted 8 December 1997

separate reports for a given patient submitted by both the physician **and** the manufacturer), when recognized by the adverse event reviewer, were eliminated from the study. The injection site necrosis and non-injection site necrosis groups do **not** contain duplicates. The largest group, 1443 reports of injection site reactions, may contain a few duplicates. Adverse event reports that described more than one of the adverse events reviewed (e.g., both, injection site reaction and necrosis) were categorized as the more clinically significant.

For most of the adverse event reports reviewed, the data consisted of the information contained in the adverse event reports as originally submitted to FDA. In some cases, however, the information was supplemented by one or, both of the following means: (1) telephone follow-up with the initial reporter and/or other persons familiar with the patient's adverse event (e.g., patient, physician, pharmacist) and (2) additional records (e.g., hospital discharge summaries, biopsy reports) subsequently forwarded to FDA by those persons.

Results

A total of 9032 adverse event reports for interferon beta-1b was received by FDA between July 1993 and January 1996. Of these, 2974 were indexed with 'key words' denoting the adverse events selected for this review. Hard copies of the adverse event reports available from the reviewer or the database archives were retrieved and known duplicates were omitted. Reports were reviewed for 1443 (58%) of the injection site reactions, 212 (92%) of the injection site necroses, and 10 (100%) of the non-injection site necroses. The number of reports of each adverse event reviewed is given in Table 1. Although the relative frequencies and percentages of the non-injection site necroses are included in the following text and Tables, we acknowledge that their significance and interpretation must be tentative, given the relatively small number of these adverse event reports in our review.

The patient sex, patient age, and the length of interferon beta-1b treatment at the time of onset of the adverse event are likewise given in Table 1. The patient age range was similar for injection site reactions and necroses. However, the patient age range appeared to be considerably narrower for the non-injection site necroses and included neither geriatric patients nor male patients. The mean number of months between the start of interferon beta-1b treatment and the onset of the adverse event was least for the injection site reactions (i.e., 2.1 months) and greatest for the non-injection site necroses (i.e., 3.4 months). Although not presented in Table 1, 59% of all adverse events began within the first month of treatment.

The clinical presentation of the adverse events is shown in Table 2. For the injection site reactions that were characterized, 827 (57%) presented with erythema, and 439 (30%) presented with pain. Of the injection site reactions, 551 (38%) presented with a single sign/symptom. The remainder included up to eight signs/symptoms.

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Table 1 Adverse event reports reviewed by patient sex, patient age and length of interferon beta-1b treatment at the time of onset of the adverse event

	Injection site reactions (n=1443)	Injection site necrosis (n=212)	Non-injection site necroses (n=10)
Sex (%)			
Female	1253 (87%)	183 (86%)	10 (100%)
Male	154 (11%)	25 (11%)	—
N/I ^a	36 (3%)	4 (2%)	—
Ratio			
Female : Male	8.1:1	7.3:1	*
Age (year)			
Range	13-71	23-70	23-48
Median	42	47	42
N/I ^a	208 (14%)	30 (14%)	3 (30%)
Time between start of interferon beta-1b treatment and onset of adverse event (months)			
Range	≤1-29	≤1-19	≤1-7
Mean	2.1	3.1	3.4
S.D.	3.0	3.2	2.3
Median	≤1.0	61.0	≤1.0
N/I ^a	250 (17%)	35 (17%)	1 (10%)

^aN/I = information not indicated. *Ratio not calculated because of relatively small number of adverse event reports and because all patients were female

Table 2 Adverse events reviewed by clinical presentation

	Injection site reactions (n=1443)	Injection site necrosis (n=212)	Non-injection site necroses (n=10)
Sign/Symptom			
Erythema	827 (57%)	22 (10%)	—
Pain	439 (30%)	38 (18%)	—
Bruising	176 (12%)	22 (10%)	—
Edema	156 (10%)	11 (5%)	—
Discoloration	133 (9%)	2 (1%)	—
Pruritus	120 (8%)	4 (2%)	—
Ulceration	100 (7%)	22 (10%)	—
Infection	61 (4%)	25 (12%)	1 (10%)
Fasciitis	—	4 (2%)	2 (20%)
Vasculitis	—	5 (2%)	1 (10%)
Other	193 (13%)	12 (6%) ^b	—
N/I ^c	131 (9%)	—	—
No of Signs/Symptoms (%)			
1 sign/symptom	551 (38%)	120 (53%)	6 (60%)
2 signs/symptoms	403 (28%)	48 (23%)	4 (40%)
3 signs/symptoms	222 (15%)	30 (14%)	—
≥4 signs/symptoms	137 (10%)	22 (10%)	—
N/I ^c	131 (9%)	—	—

*Percentages of signs/symptoms >100.0% because >1 adverse event report included >1 sign/symptom. ^aOther = <5.0%, in decreasing order of frequency: hypersensitivity, warmth, scabbing, inflammation, scarring, dryness, lot-specific, blistering, rash, atrophy, numbness, leathery-like skin, burn-like appearance, cellulitis, psoriasis, cyst. ^bOther = <3.0%, in decreasing order of frequency: cellulitis, dryness, blistering, rash, spider angioma, thrombosis, warmth. ^cN/I = information not indicated

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Of the 19 presenting signs/symptoms for the injection site necroses reports, besides necrosis, no single sign/symptom predominated. Pain accounted for the most frequent presenting sign/symptom in 39 (18%) of the reports, followed by approximately equal percentages of infection, bruising, erythemas, and ulceration. Necrosis as the only sign/symptom accounted for 120 (53%) of the clinical presentations, but the remainder of the injection site necrosis reports included up to seven signs/symptoms.

The clinical presentation of the non-injection site necroses was less diverse. These presented with necrosis alone in six of the 10 adverse event reports and with either fasciitis, infection, or vasculitis in the remainder.

The treatment received for the adverse events is shown in Table 3. Across all adverse events, the relative percentages for which the treatment received was not indicated were between 48 and 77%. For the injection site reactions, 11 different treatments were reported (e.g., antibiotics, discontinuation of interferon beta-1b, change in injection technique, steroids). No single treatment predominated, and the number of treatments received ranged from 1-4.

Among the nine treatments specified for the injection site necroses, antibiotics was the most frequent, accounting for 31%, with surgery the next most frequent, accounting for 21%. The number of treatments received ranged from 1-4.

When specified, only two treatments were reported for the non-injection site necroses. Surgery was the most frequent, accounting for four of the 10 adverse event reports. Followed by antibiotics, accounting for

two of the 10 adverse event reports. The number of treatments received ranged from one to two.

Only 5% of reports contained any information about the outcome of the adverse event. Thus, there was essentially no outcome information available from the adverse events reports reviewed.

Discussion

Injection site reactions, injection site necrosis, and non-injection site necrosis were observed during the clinical trial of interferon beta-1b for relapsing remitting multiple sclerosis. Since a clinical trial involves a relatively small, select group of patients, we reviewed the adverse event reports for injection site reactions, injection site necroses, and non-injection site necroses involving interferon beta-1b in the FDA database to obtain more complete information on these adverse events since the drug has gone into general use.

The adverse event reporting system at FDA is a passive reporting system. Such systems have a number of limitations (e.g., underreporting, reporter bias, incomplete and missing information). Also, information as to the actual number of patients receiving this product is not available so that incidence rates cannot be calculated.² Nevertheless, this reporting system can provide useful information and provide leads for the generation of hypotheses.

We found that the greatest percentage of adverse events began within the first month of interferon beta-1b treatment. The longest time until onset of the adverse event was 29 months. On average, the least clinically significant (i.e., injection site reactions) required less time to develop than the more clinically significant (i.e., injection site and non-injection site necroses). The relative likelihood of clinically significant adverse events (e.g., requiring medical intervention, resulting in irreversible and permanent sequelae) was greatest for non-injection site necroses. In patients with more than one type of adverse event, no invariant clinical course or evolutionary pattern was observed.

Females appeared to be at greater risk, overall, than males for these adverse events, as shown by the composite 8.1:1 female:male ratio in this review. The sex ratio for multiple sclerosis is estimated to be 2:1 female:male.⁷ We found no information in our review or from the clinical trial results to suggest what, if any, factors might cause females to be more prone than males for these adverse events. Some or all of this sex differential could be due to artifacts (e.g., if greater proportions of females were treated with interferon beta-1b, if females were less compliant with the recommended injection site rotation pattern, if females were more likely to report an adverse event).

Although the number of reports of non-injection site necrosis was small and allowed only tentative interpretations, the age range of patients who experienced non-injection site necroses might be narrower than that for both injection site reactions and necroses. Also, no male or geriatric patients were included.

The treatment received for the adverse event was available for approximately 50% of the cases re-

Table 3 Adverse events reviewed by treatment received

	Injection site reactions (n=1443)	Injection site necroses (n=212)	Non-injection site necroses (n=10)
Treatment*			
Antibiotics	104 (7%)	65 (31%)	a (20%)
Discontinued interferon beta-1b	89 (6%)	9 (4%)	-
Steroids	74 (5%)	28 (13%)	-
Surgery ⁱⁱ	12 (1%)	44 (21%)	4 (40%)
Other	167	14 (6%) ⁱⁱ	-
N/I ⁱⁱ	(12%) ^b	102 (48%)	6 (60%)
	1113 (77%)		
No of Treatments received			
1 treatment	231 (16%)	64 (30%)	2 (20%)
2 treatments	64 (4%)	34 (16%)	2 (20%)
3-3 treatments	16 (1%)	12 (6%)	-
N/I ⁱⁱ	1113 (77%)	102 (48%)	6 (60%)

*Percentages of treatments >100.0% because >1 adverse event report included >1 treatment. "Surgery=incision/drainage, debridement, excision, and/or skin grafting. "Other = @ <3.0% in decreasing order of frequency: change in injection technique, analgesic, antihistamine, decreased interferon beta-1b dosage, vitamin, anesthetic, interferon alfa. "Other = @ <3.0% in decreasing order of frequency: change in injection technique, analgesic, decreased interferon beta-1b dosage, vitamin, anesthetic, antihistamine, interferon alfa.

Table 4 Comparison of injection site reaction, injection site necrosis, and non-injection site necrosis adverse events from interferon beta-1b clinical trial and FDA review

	Clinical trial ^{3,6} (n=124)	FDA review (n=1665)
Sex (%)		
Females	68.4	86.8
Males	30.6	10.8
N/A ^a		2.5
Female: male ratio	2.3:1	6.1:1
Age (year)		
Range	18-50	13-71
Mean	36.0	43.1
S.D.	7.9 ^b	9.0
Time between start of interferon beta-1b treatment and onset of adverse event		
Median	7 days	≤1 month
Adverse event reports (%)		
Injection site reaction	85	30.1
Injection site necrosis	5	2.7
Non-injection site necrosis	2	0.2

^aN/I=information not indicated. ^bValue extrapolated from data provided⁵

viewed. And since only 5% of the reports contained information as to outcome of the adverse event, no assessment can be made of treatment efficacy based on the adverse event reports reviewed for this study.

Given the known limitations of clinical trial,⁹ it is of interest to compare our results with those of the clinical trial for interferon beta-1b presented in Table 4. In general, our results were similar. The rank order of the adverse event frequencies in our review was the same as that in the clinical trial, and the time to onset of the adverse event was also similar. The lower relative percentage of adverse events in our review was undoubtedly attributable to the known underreporting in a passive reporting system such as FDA's.² This underreporting cannot be readily estimated and is influenced by numerous variables (e.g., severity of adverse event; number of patients under treatment, estimated by the manufacturer to have been 30,000 in November 1995).^{2,3} The lower relative percentage of injection site reactions, in particular, may be in part attributable to an under-sampling of adverse events from the FDA database, due to limitations of the 'key word' indexing of adverse event reports (i.e., maximum of four 'key words' per adverse event report). This under-sampling, though anticipated, could neither be compensated for a priori nor estimated.

As might be expected, our results showed a wider age range of patients than in the clinical trial. This can presumably be accounted for by the postmarketing phenomenon, that patients receiving interferon beta-1b

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after FDA licensure would be expected to be more demographically and clinically diverse than those in the clinical trial, the latter having been selected according to pre-set eligibility criteria.^{2,4}

Our results showed a much higher relative female: male ratio of 8.1: 1 than in the clinical trial. In the clinical trial the female: male ratio was 2.3: 1, which is about the same as the estimated sex ratio for the incidence of multiple sclerosis.⁴

These findings emphasize that injection site reactions, injection site necroses, and non-injection site necroses warrant careful and continued clinical monitoring.^{6,7} Such reactions should continue to be reported to the manufacturer or the FDA MedWatch program (1-800-332-1088) so that more definitive information on the epidemiology, treatment, and outcome of these adverse events may be obtained. In particular, the apparent female preponderance of the adverse events found in this review deserves further study.

Acknowledgements

We wish to express our appreciation to the following individuals who contributed to this review: Ms Jennifer Bateman, for data entry; Mr Thomas Lively, for data analysis; and Drs Susan Ellenberg, Marcel Salive, and Andrew Lerner for review and comment.

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